UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,860	02/18/2005	Takeshi Koizumi	Q86151	2817

23373 7590 05/14/2008

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
05/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,860	KOIZUMI ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-47,49 and 50* is/are pending in the application.

4a) Of the above claim(s) *41,42,45-47 and 49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-40,43,44 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/14/2008 has been entered.

Status

Claims 38-47, 49 and 50 are pending. Of these, claims 41, 42, 45-47 and 49 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/09/2007.

The rejection of claims 39, 40, 43 and 50 under 35 U.S.C. 112, 2nd paragraph made in OA 11/14/2007 is withdrawn in view of Applicant's amendment.

The rejection of claims 37-40, 43, 44, 48 and 50 under 35 U.S.C. 112, 1st paragraph made in OA 11/14/2007 is withdrawn in view of Applicant's amendment. In particular, claims 37 and 48 have been cancelled. Furthermore, the claims as amended are structurally limited in such terms that the disclosure as filed would reasonably convey to one of skill in the art that Applicant was in possession of the claimed primer.

The rejection of claims 37-40, 44 and 48 under 35 U.S.C. 102(b) over GenBank® GI:16565115 made in OA 11/14/2007 is withdrawn in view of Applicant's amendment.

In particular, claims 37 and 48 have been cancelled. Furthermore, Applicant has amended the claims to require that the primer is not more than 40 nucleotides in length.

The rejection of claims 37-40, 43, 44, 48 and 50 under 35 U.S.C. 102(b) over Random Primer 24 (New England Biolabs) made in OA 11/14/2007 is withdrawn in view of Applicant's arguments, which are found persuasive. In particular, claims 37 and 48 have been cancelled. As to the remaining claims, the examiner is persuaded that, however probable, the facts do not support an adequate finding of inherency, since even if the probability is *virtually* 100%, it is still only a probability.

All rejections set forth are new rejections, and are the only rejections pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 38-40, 43, 44 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 requires that the claimed primer be not more than 40 nucleotides in length. Claim 38 also requires that the claimed primer comprise a region of at least 15 continuous nucleotides of SEQ ID NO:3 and that said region comprises at least two of the following positions of SEQ ID NO:3: positions 9, 81, 138, 153, 172, 180, 208, 228, 237, 288 and 540. It is noted that positions 9, 81, 288 and 540 are each more than 40 nucleotides away from any other of the recited positions. Hence, it would be impossible

for the claimed primer to comprise any of positions 9, 81, 288 and 540 and still satisfy the other requirements of the claim. Since claims 39, 40, 43, 44 and 50 depend directly or indirectly from claim 38, they are rejected for the same reasons.

Claim 50 is further rejected under this section on the grounds that the claim recites a kit (which is a product) wherein the primer of any one of claims 38-40, 43 and 44 "is used" (which is a method). This begs the question, would a kit comprising the primer fall within the scope of the claim only if the primer is used? Would one who makes the kit and sells it to someone else be infringing the claim, since the seller did not "use" the primer? Applicant is advised to simply recite that the kit comprises the primer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 38-40 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al (Applied and Environmental Microbiology 65(3):1141-1144; 1999) in view of Torriani et al (Applied and Environmental Microbiology 67(8):3450-3454; 2001), Stine et al (Infection and Immunity 68(12):7180-7185; 2000; cited on the IDS of 02/18/2005) and GenBank Accession Numbers AF311535, AF311574-311576, AF311578-311583, AF311585-311586, and AF311589-311596 (cited on the IDS of 07/11/2006, each of which was publicly available on 1 November 2001).

With regard to claims 38-40 and 44, Warner teaches a method for discriminating *Vibrio* species from one another, as well as differentiating between *V. vulnificus* strains using randomly amplified polymorphic DNA analysis (see entire article).

Warner does not teach primers corresponding to the claimed primers, which Applicant made based on differences in the sequence of the *recA* gene between *V. vulnificus* and other *Vibrio* species.

It was known in the prior art to design species-specific primers, based on differences in the sequence of the *recA* gene among related bacterial species, in order to differentiate among the related species. Torriani teaches this with respect to discriminating among species of the genus *Lactobacillus*. Of randomly amplified polymorphic DNA-PCR (the method used by Warner), Torriani states: “such methods are not suitable for routine identification requirements” (page 3450, column 1, second paragraph). As an improvement over such methods, Torriani teaches: "PCR using

species-specific oligonucleotides designed based on phylogenetic molecular markers could be a useful approach...It has been proposed that the *recA* gene could be used as a phylogenetic marker, and it has already given satisfying results for many bacterial genera..." (page 3450, column 2, first full paragraph, citations omitted). Torriani then goes on to design such primers for *Lactobacillus* (see entire article). It is noted that Torriani's primers were at least 15 nucleotides and not more than 40 nucleotides in length (page 3451, column 2, "Multiplex PCR assay").

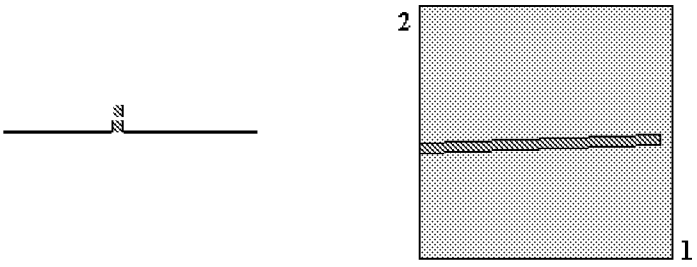
Stine sequenced *recA* from 113 *Vibrio cholerae* strains and closely related species, including *Vibrio vulnificus* (see abstract and Table 1). Stein states: "The locus chosen for study was *recA* because it has been shown to be useful for estimating phylogeny, in contrast to some other genes" (page 7180, column 1, second paragraph, citations omitted). Stine also remarks: "As expected, the *Vibrio vulnificus* and *Vibrio parahaemolyticus* sequences formed out-groups" (page 7821, column 1, first full paragraph). Hence, Stine provided a reasonable expectation of success in using *recA* sequence differences to discriminate *Vibrio vulnificus* from other *Vibrio* species.

The GenBank Accession Numbers represent a collection of *recA* sequences from 20 strains of *Vibrio vulnificus* submitted to the GenBank database by Benagli and colleagues on 6 October 2000, and which were made publicly available at least as of 1 November 2001. To confirm that this collection of known *V. vulnificus recA* sequences would have provided the information necessary to arrive at a *V. vulnificus*-specific primer as set forth in the claims, the sequence of SEQ ID NO:17 (Applicant's elected

SEQ ID NO, as recited in claim 44) was compared to one of the GenBank sequences (AF311535, which is GenBank GI:16565115):

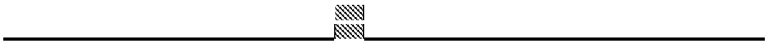
Sequence 1: SEQ ID NO:17
Length = 21 (1 .. 21)

Sequence 2: gi|16565115|Vibrio vulnificus strain 9067-96 recombinase A (recA) gene, partial cds
Length = 543 (1 .. 543)



NOTE: Bitscore and expect value are calculated based on the size of the nr database.

NOTE: If protein translation is reversed, please repeat the search with reverse strand of the query sequence.



```
 Score = 39.9 bits (20),  Expect = 0.045
 Identities = 20/21 (95%), Gaps = 0/21 (0%)
 Strand=Plus/Plus

Query  1    CCTGTGTATGCGAAGAARCTT  21
            ||||||||||||||||| |||
Sbjct  238  CCTGTGTATGCGAAGAAGCTT  258
```

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method used by Warner by following the example of Torriani, who described an improved method of discriminating among bacterial species using species-specific primers based differences in the *recA* gene among those species. Therefore, one of ordinary skill would have been motivated to use the known *Vibrio vulnificus recA* sequences available in GenBank to design species-specific primers for the purpose of discriminating *Vibrio vulnificus* from other

Vibrio species. Both the disclosures of Torriani and Stine explicitly suggest *recA* as a marker for discrimination among species of related bacteria.

In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court stated: "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill" (at 1389). The same rationale would apply to improving upon one prior art method based on a similar improvement to another prior art method (see MPEP 2143(C)). Torriani clearly recognized that species-specific differences in *recA* had allowed discrimination among other related bacteria, and so applied this knowledge to *Lactobacillus*. Likewise, the ordinary practitioner would have been motivated to apply the knowledge from Torriani's disclosure to the design of similar primers for *V. vulnificus*.

In following this course, one would have inevitably identified which nucleotides in *recA* were specific for *V. vulnificus* (as well as which were specific for other *Vibrio* species). As these differences were not numerous, one would have been guided by those "specific" bases when choosing appropriate species-specific primers for *V. vulnificus*. As the Court noted in *KSR*, "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress" (at 1389). Such is the case here, for Applicant has arrived at the claimed primers simply by applying what others have done before with other microorganisms to *Vibrio vulnificus*.

While the work involved may have been significant, it does not represent "real innovation".

Furthermore, one would have been motivated to incorporate as many "specific" bases into the primers as possible, in order to maximize the specificity of the primer. Hence, one would have been motivated to incorporate "at least two" and possibly more depending on how closely spaced the "specific" bases were to one another.

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al (Applied and Environmental Microbiology 65(3):1141-1144; 1999) in view of Torriani et al (Applied and Environmental Microbiology 67(8):3450-3454; 2001), Stine et al (Infection and Immunity 68(12):7180-7185; 2000) and GenBank Accession Numbers AF311535-AF311596 as applied to claims 38-40 and 44 above, and further in view of Yokoyama et al (US 2002/0098487).

The teachings of Warner, Torriani, Stine, and GenBank have been discussed. These references would not necessarily have directed one to design the primers so as to place a base specific for *Vibrio vulnificus* at the 3' end of the primer.

Yokoyama is yet another prior art example of using sequence differences among species, this time using difference differences in the cytochrome b gene to discriminate among species of the genus *Aspergillus* (see para [0008]). Yokoyama further teaches (para [0019]):

"…the present inventors amplified the genes of a number of strains of the fungi belonging to the genus *Aspergillus*, determined the sequences of the amplified genes

and carefully compared the sequences, to discover sites each of which is specific to each species. Examples of the specific sites (1 base) include the 24nt "T", 99nt "T", 144nt "T"…[etc]… By using an oligonucleotide whose 3'-end is the above-mentioned specific site (1 base) as a primer for amplifying the nucleic acid, the mitochondrial cytochrome b gene fragment of the corresponding species alone is amplified. Therefore, each species may be specifically detected, in other words, identification of the species may be carried out."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to design the *Vibrio vulnificus*-specific *recA* primers (suggested by the combined prior art of Warner, Torriani, Stine and GenBank) such that the 3' nucleotide of the primer was one of the nucleotides specifically found in *Vibrio vulnificus* (following the example of Yokoyama). Yokoyama gives express suggestion that this allows for specific amplification of the corresponding species. This would also have made common sense to one of skill in the art, since it was known that polymerases extend a primer from the 3' end, and that complementarity of the 3' base of a primer to its target was critical for successful amplification.

Claim 50 is rejected under 35 U.S.C. 103(a) as being unpatentable over Warner et al (Applied and Environmental Microbiology 65(3):1141-1144; 1999) in view of Torriani et al (Applied and Environmental Microbiology 67(8):3450-3454; 2001), Stine et al (Infection and Immunity 68(12):7180-7185; 2000) and GenBank Accession Numbers

AF311535-AF311596 as applied to claims 38-40 and 44 above, and further in view of the 1988 Stratagene Catalog.

The teachings of Warner, Torriani, Stine, and GenBank have been discussed. These references would not necessarily have directed one to incorporate the *Vibrio vulnificus*-specific *recA* primers suggested by the combined prior art of Warner, Torriani, Stine and GenBank into a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to incorporate the *Vibrio vulnificus*-specific *recA* primers suggested by the combined prior art of Warner, Torriani, Stine and GenBank into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches advantages of kits: "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for

everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control." (page 39, column 1)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

scw

/Young J Kim/
Primary Examiner, Art Unit 1637